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ALLERGIC SKIN DISEASES (L FONACIER, SECTION EDITOR)

Non-Pharmacologic Therapies for Atopic Dermatitis

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Abstract Atopic dermatitis (AD) continues to present significant therapeutic challenges, especially in severe cases. Navigating the line between risk and benefit can be difficult for more powerful medications such as immunosuppressants, but non-pharmacologic treatments are often overlooked and underutilized. Creative application of these more physical therapies can serve to minimize the pharmacologic treatments and their side effects, and possibly even create synergy between modalities, to maximize benefit to the patient.

Keywords Atopic dermatitis · Therapy · Non-pharmacologic · Physical · Eczema · Cryotherapy · Hydrotherapy · Climate · Temperature · Balneotherapy · Phytotherapy · Moisturization · Diet · Nutrition

Introduction

Atopic dermatitis (AD) is a chronic relapsing pruritic skin disease that often begins in the first years of life, but affects patients of all ages. Its etiopathogenesis is complex and still not fully elucidated, but is likely related to skin barrier dysfunction, allergic/immunologic aberrations, and pruritus [1].

Fittingly for such a complex and multifactorial disease, there are a tremendous number of pharmacologic treatments for AD. Anti-inflammatory agents, antibacterials, anti-pruritic agents, and those with multiple modes of action such as coal tar, define the landscape. However, there is another world of non-pharmacologic treatments that is perhaps nearly as extensive, though less well known, and likely underutilized by some clinicians. These treatments include textiles that can soothe, physical methods such as cooling the skin, ultraviolet light, moisturizers, water and bathing techniques, hypnosis, biofeedback, and other behavioral techniques, to name a few.

As non-pharmacologic interventions encompass a large area, this review will be limited to those with clinical trials, and will present illustrative studies rather than attempting to systemically review each modality. There are also some gray areas when it comes to defining "non-pharmacologic" modalities; indeed, some moisturizers and barrier-repair creams present suspiciously drug-like mechanisms, while phototherapy and many botanical agents can be considered pharmacologic or non-pharmacologic depending on how one chooses definitions. For this review, I will focus on selected physical, behavioral, and psychological interventions that may not be discussed in other settings but are worthy of further exploration.

Textiles and Clothing

It has long been known that wool intolerance is a feature of atopic dermatitis [2, 3]. This raises the question of whether certain textiles could actually be helpful in managing AD. Cotton clothing has often been the mainstay of recommended material for patients with AD [4]. However, in the past decade, a number of interesting studies suggest there may be superior alternatives.

In 2007, a study of 22 children with AD compared those given a special silk garment to a control group given a cotton garment worn over the cubital region.. At weeks 4, 8, and 12, a significant decrease in the local eczema severity (SCORAD) was found in the experimental group [5]. Silk is hypothesized to aid wound healing by enhancing collagen synthesis and reducing edema and inflammation; this specially-coated silk also has antimicrobial properties which may play an additional role [6].

A more provocative study of 15 children reported that after 7 days of treatment of split-garments (one side made of

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special silk, the other of cotton), there was an equally significant decrease in eczema on both sides—despite the fact that. on the cotton side. the patients were allowed to use topical corticosteroids [7]. The somewhat optimistic conclusion that the silk clothing proved to be *comparable* to topical steroid treatment raised criticism in particular, and a review in 2009 of all of the studies with this specialized silk clothing noted that this trial (as well as the other 3 notable trials) were all poorly reported and involved very small numbers of patients, making them insufficiently powered to make claims such as equivalency to topical corticosteroids and cautioned that further skepticism is required [8]. Still, for a safe, gentle modality without side effects, medical silk-based garments remain a reasonable consideration.

Silver-coated textiles have been shown to have an antibacterial effect on *Staphylococcus aureus*, an important colonizer in AD which may also have implications in triggering inflammation [9]. A study of 68 patients with AD compared wearing silver-coated clothing to cotton garments and found that there was significant improvement of the eczema in the silver-coated group at 1 week, with comparable comfort [10].

A similar study of 30 patients compared a silver-coated textile, a silver-free textile, and a topical corticosteroid, and used a randomized parallel-group that allowed all patients to wear the silver-coated garment in the second phase, and then no textiles in the third phase. The study found that the groups using the silver-coated clothing had significantly decreased pruritus and reduction of eczema severity, as well as decrease in the use of the topical corticosteroid [11].

A recent randomized double-blind controlled study of 19 children with AD compared placebo clothing to a new textile made of "silver-seaweed-cotton" fibers. The study found that by day 7 there was significant improvement in the SCORAD in the treatment group, and that by day 90, there was 45 % decrease in SCORAD as well as reduced pruritus and improvement in sleep [12].

Although more robust studies need to be done on these textiles, there are promising data that beyond simply avoiding wool, silk and silver-impregnated clothing could potentially make a difference in treating AD. Several brands of silver-coated clothing and silk-based garments are available that are targeted towards eczema. They tend to be fairly expensive, ranging from $60–80 USD for some of the different pajamas or body suits designed for infants, but may be washed multiple times without losing efficacy [13–15].

Climate and Temperature

There is a body of evidence to support the connection between cold and dry climate factors and AD [16]. Remarkably, the exact opposite has also been convincingly demonstrated, with heat and humidity also being associated with flares [17, 18]. Finally, a study of 56 children with severe AD evaluated the effect of moving from a subarctic/temperate climate in Norway to a sunny subtropical climate in Gran Canary for 4 weeks. They found that there was significant improvement in SCORAD and quality of life for the patients who spent time in Gran Canary compared to controls [19]. This suggests that what has long been reported by patients and families is probably true: temperature changes and extremes can worsen AD, but winter tends to be worse.

A unique and somewhat incredible study using whole-body cryotherapy in a specialized chamber at temperatures down to −110 °C (−166 °F) three times weekly demonstrated significant benefit to patients with severe atopic dermatitis [20]. The authors hypothesized that the effect was related to reduced nerve conduction velocity and decreased synthesis of acetylcholine in the nerve ganglia, both of which could influence pruritus. The need of a specialized chamber and the thrice-weekly treatment regimen makes this approach much less feasible, unfortunately.

A more recent study examined the effect of a water-filled passive cooling pillow on sleep quality in patients with severe head and neck AD [21]. While there was a trend towards improvement in sleep quality and severity of the AD in the experimental group, the study size was small and the results were not statistically significant. A portable home-based cooling therapy like this could have therapeutic potential and is an area warranting further investigation.

Water and Bathing (Balneotherapy)

As increased transepidermal water loss is one of the fundamental characteristics of AD, it is not surprising that there are interventions involving water and bathing. Spa therapy and balneotherapy are ancient practices, but emerged as modern treatment modalities in the 1800 s in Europe [22]. Generally, these involve immersion in mineral water baths or pools, often in the context of warm weather (climatotherapy), sun exposure (heliotherapy), and a generally relaxed atmosphere away from the stressors and routines of everyday life, it is important to add [23].

An open, randomized trial in Trentino, Italy, of 104 children with mild to moderate AD received either balenotherapy (total immersion into thermal spring water rich with calcium, magnesium, and other minerals for 20 min once daily) for 2 weeks, or topical corticosteroid treatment for the same period. Both groups had significant improvement in eczema severity and quality of life measures, with the corticosteroid group showing a significantly larger reduction in the SCORAD, but with similar effect in the quality of life indices (CDLQI and FDIQ). At month 4, however, there was a significant difference in the number and duration of relapses favoring the balneotherapy group [24].

Similarly, a study of 386 adult and pediatric patients with AD examined the effect of a 3-week course of Avène hydrotherapy (a mineral spring in the south of France with an associated spa) revealed significant improvements in quality of life that persisted at months 3 and 6 post-therapy [25]. Subsequent studies have proposed mechanisms for the improvement that include anti-inflammatory modulation of IL-8, reduced staphylococcal colonization, and inhibition of TNF-alpha-induced adhesion molecules [26, 27].

The conditions at the Dead Sea, Israel, the lowest elevation on land and with hypersaline waters, have long been found to be helpful for skin diseases. Indeed, in a study of 49 AD patients treated at the Dead Sea that consisted of gradually increasing sun exposure and bathing in the sea for 20 min twice daily, along with emollients and a stress-free environment, found a significant improvement in the eczema severity and quality of life [28].

While encouraging a spa vacation at the Dead Sea or in southern France is not possible for most patients with AD, several attempts have been made to recreate these conditions.

Heinlin et al. performed a randomized controlled study to examine synchronous balneophototherapy (sBPT) which uses narrow band UVB light while bathing in a 10 % Dead Sea salt solution to mimic the Dead Sea environment. They found that compared to phototherapy alone with narrow band UVB, the sBPT group performed significantly better (26.2 % improvement) on the SCORAD after 35 sessions [29].

Beyond this, there is some evidence to suggest that simply bathing in salt water may have some physical and pharmacological effects. Salt water with added minerals, such as magnesium, calcium, and bromide, may modulate Langerhans cells, inhibit 5-lipooxygenase, and inhibit Th1 lymphocytes [30]. A German study compared using a 15 % salt water solution with Dead Sea minerals to a 3 % simple sodium chloride solution, and reported better effects in the former group after 4 weeks [31].

Paradoxically, despite all these studies suggesting *improvement* with mineral-rich water, there are epidemiological studies and anecdotal reports connecting hard water (another name for mineral-rich water) with the *worsening* of AD, prompting a study to test the effect of a water softener on AD. A large randomized trial of 336 children found, at 12 weeks, no significant difference in eczema improvement between the groups, despite the fact that families were not blinded to their treatment allocation, something that would be expected to increase any perceived effect [32].

There may be something more to mineral baths, but the effect beyond the phototherapy and relaxation is probably modest at best.

Phototherapy

Perhaps the most important part of visiting the Dead Sea (and other similar experiences) is the sunlight. Phototherapy—the use of ultraviolet light therapeutically—has long been shown to be effective for AD [33].

Phototherapy is thought to work by a number of mechanisms, including immunomodulation via lymphocyte apoptosis, depletion of Langerhans cells in the skin, and suppression of proinflammatory cytokines [34]. NB-UVB has also been shown to be very effective in repleting vitamin D deficiency, which may also play a role in AD [35, 36]. Finally, NB-UVB appears to have effects on certain types of pruritus, a central component of AD, which may also explain some of its benefit [37].

There are many details that remain to be optimized in phototherapy, however, from the type of light [ultraviolet A (UVA), ultraviolet A1 (UVA1), broadband ultraviolet B (UVB), narrowband ultraviolet B (NB-UVB), etc.] to the many subtle refinements in the dosing and timing regimens. An excellent systematic review in 2007 summarized that UVA1 (340–400 nm light) appears to be faster and more effective than combined UVA and UVB light for treating acute AD flares. NB-UVB (311 nm light) appears more effect than UVA or UVA1 for managing chronic AD [38]. A more recent study, in 2009, further supported this by demonstrating that NB-UVB and UVA1 appear to be equally effective in patients with moderate to severe AD, a helpful report given the rarity and expense of UVA1 units and the relative commonality of NB-UVB phototherapy units [39].

For refractory cases or when corticosteroid dependence is developing, NB-UVB phototherapy is a relatively safe treatment that can postpone or avert the need for systemic medications in select patients, and may even have remittive properties in AD as it does for psoriasis [40].

Moisturization

AD is perhaps the “poster child” for moisturizers, and there is good evidence that using moisturizers more frequently directly relates to improvement in eczema severity [41]. It follows then that regular emollient use also appears to have a steroid-sparing effect in AD [42]. A recent study of 191 children with mild to moderate AD found that emollient use alone had highly significant effects on the eczema severity as well as parental quality of life [43].

Thus, it seems clear that moisturizers are an important non-pharmacologic therapy for AD. The question arises: which one is best? The answer is not easy. This is a complex area of dermatology, with many recent innovations and advancements, some of which are suspiciously drug-like in their claims.

At least three main causes of xerosis have been defined: deficiency of natural moisturizing factor (NMF); deficiencies in skin barrier lipids such as ceramides; and a deficiency in aquaporin water channels [44]. Because of these complexities, a full exploration into this area is beyond the scope of this paper.

Attempts have been made to better categorize the morass of moisturizers, including a recent study that mapped out their pH and a measurement called "hydrophilic index", an attempt to quantify how "greasy" they might feel [45]. However, there remains very little comparative data in this domain.

Even the frequency of application and the timing after bathing remain mostly unelucidated. An often-cited small paper by Chiang and Eichenfield concluded that bathing without moisturizer could decrease skin hydration, while moisturizer application immediately after bathing provides some hydration benefits, and using moisturizer on dry skin appears to have the most dramatic effect on hydration [46].

The so-called "barrier repair creams" may be difficult to distinguish from over-the-counter (OTC) moisturizers, but are generally available in the US as prescription 510(k) devices, a designation that was initially used for medical equipment such as insulin pumps and pacemakers [47•]. Although there is a fairly wide range of these creams, many contain one or more of the following ingredients, each of which has measurable effects on skin barrier function or inflammatory mediators: ceramides, hyaluronic acid, licorice extract, dimethicone, and palmitoyl ethanolamide; all of which can also be found in OTC formulations [47•].

As these are prescription products, they tend to be priced as such, calling their value into question, even if they are indeed superior to regular moisturizers. A clever randomized controlled trial compared two leading barrier creams (one known for containing licorice extract, the other for containing ceramides) to a petroleum-based OTC moisturizer. They found that the OTC product was 47 times more cost-effective than the barrier repair creams [48].

Moisturizers are a fundamental part of AD therapy. It seems reasonable to recommend a simple, affordable OTC product and, when possible, to allow the patient to consider a variety of emollients to identify the best fit for his or her skin [49]. From lighter creams such as Aveeno, CeraVe and Cetaphil, to the heavier and greasier preparations such as Eucerin, Aquaphor, and petrolatum, I have seen success with the entire range of moisturizers when used regularly. And, while there is compelling scientific rational for the inclusion of ceramides and other "barrier-repair" ingredients, there is not thus far, to my knowledge, overwhelming clinical evidence for their superiority over other well-formulated moisturizers in atopic dermatitis [50].

"Wet-Wrap Therapy"

In some ways, the concept of "wet-wraps"—applying topical medication and/or moisturizer to damp skin, then applying a damp layer of clothing or gauze, followed by a dry layer of clothing or gauze and leaving in place for at least several hours—is an extension of extremely occlusive moisturization, increasing water content in the skin and improving the epidermal barrier [51]. They have the added benefit of providing a physical layer of protection from scratching; a powerful deterrent, indeed.

A review of the literature in 2006 pointed out the many variations in wet-wrap methodology, from the product applied, to the type of bandaging, to the frequency of application in the 24 publications reviewed. It concluded that wet-wraps are an effective short-term treatment in children with severe or refractory AD, and pairing the wraps with a topical corticosteroid is more effective than using emollients alone. Further, wet-wrap therapy appears to be safe for up to 14 days, and it actually decreases the amount of corticosteroid used during that timeframe [52]. Discomfort (including chills) was the main adverse event, with folliculitis as a common complication, and other infections more rarely seen. Occlusion, whether dry or wet, does, however, appear to increase the density of skin bacteria [53•].

Although not in any of the studies discussed, using a dilute bleach bath to decolonize the skin prior to the application of wet-wraps may decrease the risk of folliculitis and other infections. However, this hypothesis needs validation.

Dilute Bleach Baths

The now landmark 2009 paper by Huang et al. demonstrated significant improvement in eczema severity in an experimental group that received a dilute bleach bath (0.005 % final concentration; about 0.5 cup of 6 % bleach in a full bathtub) for 5–10 min twice weekly, compared to a placebo-bleach bath control [54]. Since then, I have seen a tremendous clinical effect in terms of eczema severity and decreased infection rate in my patients adhering to dilute bleach bath therapy.

However, there is some controversy about this simple and inexpensive technique. A commentary published soon after the report concluded: "We will not be changing our practice on the basis of these findings for most of our patients with AD. We welcome an additional larger and longer term study of a similar approach…that allows for baseline differences with outcomes such as global improvement and prevention of disease flares…" [55]. Similarly, a Cochrane review (notably written by the same senior author as the commentary) concluded in 2010: "We failed to find any evidence that commonly used antistaphylococcal interventions are clinically helpful in people with eczema that is not clinically infected." [56].

Since then, a study on a sodium hypochlorite "bleach" cleanser demonstrated some clinical improvement in a 12-week open-label study of 18 children with AD. Although difficult to judge without a control group, there was a significant reduction in the IGA eczema score at all time points, as well as a decrease in body surface area affected in the patients

studied, which are certainly promising enough to warrant further research [57].

In the meantime, it seems reasonable to recommend dilute bleach baths for patients with frequent infections or with a tendency towards open, oozing lesions, as the risks and costs are extremely low and the potential for benefit is significant.

Hypnosis/Biofeedback/Support Groups

AD can affect the entire family, beyond just the patient, and is known to have significant psychological ramifications [58]. Scratching in AD may become a behavioral, conditioned response that is elicited during times of anxiety [59].

Stress seems to play a role in the disease, opening up new possibilities for treatment [60].

A study in 1993 by Sokel examined biofeedback and hypnotherapy on eczema severity in 44 children. Those in the hypnotherapy and biofeedback groups showed a significant reduction in a severity score compared to controls at 8 and 20 weeks [61]. Progressive muscle relaxation therapy (PMR) was studied in 25 patients with AD compared to a randomized control group. After 1 month, there was improvement of pruritus, sleep, and anxiety in the PRM group but not in controls [62]. A behavioral method of habit reversal was applied to scratching in patients with AD in a randomized controlled trial in combination with hydrocortisone cream compared to hydrocortisone cream alone. While both groups improved, there was a significant difference in favor of the behavioral intervention [63].

Coping with the stress through support groups has also been studied. 32 patients were randomized to join a support group or not. After 6 months, the pattern of pruritus was significantly improved in the experimental group, as was the quality of life score [64].

While the examples reviewed are hopeful, these modalities require further study before any final conclusions can be made.

Education

Educational interventions can include written literature, audiovisual material, workshops, or more traditional didactics. In theory, they can empower patients and allow for better self-management with an improved sense of purpose and direction. Additionally, since patient adherence with topical treatments is generally poor, enhanced education also offers the possibility of improvement here [65, 66]. Notably, throughout the world, there is perhaps much greater emphasis on therapeutic education in AD than in the United States [67].

Several randomized controlled trials have demonstrated improvement with different educational measures, including a nurse-led eczema workshop on 99 new patients compared to a dermatologist-led clinic. At 4 weeks after the intervention, the mean improvement in SCORAD was significantly better in those attending the workshop, and there was also greater adherence to eczema management in the workshop group [68]. A large, multicenter randomized controlled trial of 992 patients in Germany found that education for children with AD resulted in improved quality of life and disease severity [69].

In an attempt to find less time-intensive methods of education, a 2011 study used an online video education program to improve knowledge and understanding of disease severity in AD for 80 patients, and compared this to a pamphlet of written material. A significant difference in knowledge and a greater improvement in clinical outcome was found in the video group, as well as patient reports that the video modality was more appealing [70].

Interestingly, a recent randomized controlled trial looking at a 12-week educational program for AD and psoriasis found that disease severity and quality of life improved significantly for the psoriasis patients, but not for those with AD, a difference that the authors were not able to explain [71].

Beyond improved disease understanding—a lofty goal perhaps, especially in the short term—just getting the patients to understand their treatment regimen is a critical step for adherence. A full regimen for eczema can have multiple steps, including antimicrobial treatments, topical corticosteroids, and moisturizers, as well as different potencies for the face and intertriginous areas when required. Adding another step of complexity is the fact that, once improved, a "maintenance" plan should be considered that utilizes either no or low-potency topical corticosteroids, perhaps only several days per week. This is a large amount of information to convey verbally in a short time.

A recent study examined the effect of using a written "eczema action plan" (akin to an "asthma action plan") that delineates the medications, the order of application (a point of endless questioning in the clinical realm: "Which do I apply first?"), the location of application, and, finally, a plan for when things are "flaring up" and a maintenance plan for when things are better. This was compared to verbally instructing the patients on the same information. Though it was a small study with no clinical follow-up, there were significant gains in understanding of the plan, risks, and benefits of the medications, anatomic location of medication use, duration of treatment, and adjusting treatment based on disease severity with the written action plan [72].

Education is undoubtedly a cornerstone of AD therapy. The question now is how to best deliver it, considering outcomes and cost.

Allergen Avoidance/Avoidance of Triggers

It is somewhat depressing that, with all of the great advancements in medical science, some of the fundaments of AD remain obscure in 2013. To wit, there is continued controversy

about whether AD is "atopic" at all, or to what extent this is true. A powerful review by Williams and Flohr brought this idea into stark relief by noting that as many as 50 % of patients with eczema or more show no allergic sensitizations (IgE sensitizations) in multiple large population studies, raising the question that there may be at least two subtypes of eczema [73]. Further review notes that the relationship between atopy and AD is weaker and more complex than previously suggested [74]. Indeed, some authors have taken to referring to the subtypes as "extrinsic" type (AD) and "intrinsic" type, which some call "atopiform dermatitis", since it lacks the atopic IgE sensitization features [75].

Despite this, there is reasonable science behind the idea that some airborne proteins, such as those produced by house dust mites (HDM) and cockroaches, have innate proteolytic activity and can directly impair the barrier in patients with AD, even in the absence of specific IgE-mediated allergy [76]. Beyond this, there may be activation of the protease-activated receptor-2 (PAR-2) on keratinocytes and dermal nerve fibers, which probably plays a role in itch sensation and barrier recovery [77]. Thus, the concept of avoiding allergens and irritants ("triggers") is called into question for at least a large portion of patients with AD, but is worth reviewing.

The association between HDM and eczema remains somewhat controversial [78]. While there is an association between the serum IgE to HDM levels and atopic dermatitis [79], many direct studies of the effect of reducing HDM antigens on AD are poorly controlled and difficult to evaluate. Indeed, one of the largest and most promising studies that found a significant decrease in eczema severity in the group using occlusive polyurethane-coated cotton encasings for bedding was noted to be deeply flawed: a post hoc subgroup analysis was required to find significance, and it was not randomized [80]. Additionally, there was no difference between those who were not sensitized to HDM and those who were, in terms of benefitting from the covers [78, 80]. Another relatively large, properly randomized, controlled and blinded study found no benefit from 1 year of HDM avoidance on disease activity [81].

Attempts to control exposure to antigens and irritants, such as sweat, sand, and dust, include a study of showering once daily without soap during school lunch break. They found that the bathing—presumably to remove allergens and irritants from the skin—showed a benefit in 54 children with AD over a 6-week period [82]. However, it is very difficult to attribute the benefit of daily showers to allergen/irritant avoidance alone given the many confounding factors here.

Similarly questionable is a study that examined the relationship between a high HDM-protein load on pajamas and development of AD in infants [83] and the studies that show frequent vacuuming of the house may decrease the severity of AD [83, 84].

Despite the compelling "common-sense" nature of these recommendations, there is simply not enough good data here to support such allergen control measures universally, although they may be reasonable in certain circumstances.

Immunotherapy

Closely related to allergen avoidance is the concept of immunotherapy. If one has an allergic trigger for eczema, it would follow that desensitization to that trigger should improve the eczema. The recently published practice parameter for atopic dermatitis assigns a strength of recommendation "B" to immunotherapy for AD [85].

A review in 2006 suggested that significant improvement could be seen in AD patients who received subcutaneous immunotherapy versus controls [86]. A more recent analysis from 2012 highlights the variability in study design and outcomes, but concludes that allergen-specific immunotherapy has potential to improve AD if type I sensitizations are present [87].

Interestingly, in one double-blind, placebo-controlled study of 48 children with AD treated with dust mite sublingual immunotherapy, the mild-to-moderate severity group showed more impressive improvement than the severe group, suggesting that the effect may be too small to make a significant difference in more severe cases [88].

Because of the variations with study design, immunotherapy regimens, and outcomes, immunotherapy remains more of a niche treatment for specific, motivated patients.

Diet and Nutrition

Of all the aspects of AD, diet continues to be one of the most contentious, with many families (and healthcare practitioners) promoting the idea that foods are the "root cause" of eczema [89]. While a very appealing concept—simply cut out certain foods and your skin will be clear!—the literature and clinical experience do not bear this out, sadly. Complicating this, however, is the fact that nearly one-third of moderate-to-severe AD patients have verifiable food allergies (type I hypersensitivity with resultant hives, angioedema, or anaphylaxis), which could certainly act as trigger for an AD flare [90].

However, a piercing study by Thompson and Hanifin nicely demonstrates that most (a resounding 80 %) of the concerns about foods that *do not* result in a type I hypersensitivity response, but are thought to exacerbate AD, disappear once better control of the eczema is achieved [91]. Indeed, more than any other study, this shines light on the complex area of food allergy and AD, and emphasizes the dangers of conflating IgE reactions with exacerbation of AD.

There have been a number of trials looking at dietary exclusions to improve AD in adults and children. An excellent review by Bath-Hextall et al. in 2009 summarized the current literature as follows:

- There is some evidence to support the use of an egg-free diet in infants with suspected egg allergy who have a positive specific IgE to eggs in the blood.
- Studies excluding foods in unselected people with AD (i.e., those with uncertain IgE status) did not show benefit.
- The lack of benefit for unselected patients was notable as there may be other non-allergic mechanisms (such as non-specific inflammation) whereby food can worsen AD; that this was not shown suggests that these contributions, even if present, are likely small [92].

Since then, there has been an increasing focus on gluten-free diets, even for those who are clearly not gluten-sensitive on laboratory testing [93]. One provocative but small study found that 30 % of adults with AD had detectable antibodies to gliadin compared to only 6.5 % in the general population [94]. Another study in 2004 looked at over 1,000 patients with celiac disease and found that AD was about three times more common in these patients than in the general population. Fascinatingly, however, 1 year on a gluten-free diet did not change the amount of AD or allergies in the patients in the study [95]. Despite the lack of data, many patients continue to ask about gluten-free diets; perhaps larger prospective studies will shed more light on this interesting area.

Type I hypersensitivity (urticaria and angioedema) is fairly straightforward to observe and can be tested with reasonable certainty. Atopic dermatitis flares after food challenge is much more difficult to study due to the delay and the intrinsic variability of the disease. Further obfuscating this area of research is a third concept of "food intolerance" that is perhaps somewhat dubious [96], but appears to be a non-immunologic—or at least a non-specific immunologic—reaction to certain foods [97]. It is likely that there are individuals with each of these subtypes of food reactions, and perhaps some with more than one. Until there is better understanding of these relationships and a more clear demarcation between these putative subtypes, I anticipate continued debate and confusion.

Clearly there are patients who find great benefit with specific food avoidance and this cannot be denied. However, when things continue to escalate to the point of malnutrition and obsession over multiple foods, despite ambiguous testing and no clear relief from dietary exclusion, it can be more deleterious to the patient than the AD itself [98].

Vitamin D

Vitamin supplements walk the line of pharmacologic therapy. They also open a veritable Pandora's box of discussion points. I will limit the review of supplements to Vitamin D alone, something that has fairly compelling data, although not much of it.

A small but impressive study of vitamin D supplementation in children with winter-related AD by Sidbury et al. postulated that part of the effects of sunlight on AD may be due to increasing vitamin D, and demonstrated significant improvement with vitamin D supplementation versus placebo [36]. A recent review analyzed 10 articles on the role of vitamin D in AD (culled from 58 articles total) that specifically addressed this relationship. They concluded:

- There is an inverse relationship between vitamin D levels and the severity of AD.
- Repletion with vitamin D promotes the epidermal barrier.
- Clinical trials suggest a therapeutic benefit from vitamin D supplementation, though the trials are small and limited [99].

Given the relative safety of vitamin D supplementation and its low cost, it seems reasonable to suggest this at least for patients who report worsening in the winter months, until larger studies can further validate this claim.

Probiotics

The concept that beyond simply causing infection, bacteria can actually drive the immune response when colonizing the skin, has shaped thinking about bacterial balance in the body and on the skin [100]. Probiotics can be defined as live microorganisms that are the same or similar to those found naturally on the body and may be beneficial to health [101].

Probiotics have been shown to be of benefit in traveler's diarrhea, antibiotic-associated diarrhea, and irritable bowel syndrome [102–104]. But what about in AD? An exciting paper in 2001 demonstrated that the probiotic *Lactobacillus rhamnosus* GG appeared to reduce the development of AD in at-risk infants through the age of 7 years, when studied in a randomized, placebo-controlled trial of 132 children [105]. Several years later, a similarly enthusiastic paper showed that probiotics (*Lactobacillus fermentum* VRI-033) given twice daily to 57 children with moderate-to-severe AD resulted in significant improvement versus placebo [106].

Despite these promising starts, a study in 2008 found no reduction in incidence or severity of atopic dermatitis with probiotic supplementation; indeed, they actually uncovered an association between probiotics and episodes of wheezing bronchitis [107]. Notably, in this study, only breastfeeding mothers were supplemented with the probiotic (*Lactobacillus GG*) 4–6 weeks before delivery until 6 months after delivery.

A more recent study found that supplementation with strains of *Lactobacillius rhamnosus*, or *Lactobacillus paracasei* and *Bifidobacterium longum* in combination, to the pregnant and breast-feeding mother with positive skin prick allergies reduced the risk of developing eczema in infants [108].

Since then, there have been many studies with different strains of probiotic, dosage, and timing, making for a very heterogeneous group of studies. A meta-analysis of 14 trials suggested a moderate effect of probiotics on decreasing the incidence of AD [109].

Conversely, a review of the evidence for prevention and treatment of eczema examined 7 randomized controlled trials on prevention and 12 on treatment of AD and found conflicting results. They concluded that there was not convincing evidence to recommend probiotics for AD prevention or treatment [110].

All of this leaves us in a quandary with far more questions than answers: which strain, what dosage, what frequency, what timing? My own experience has been that, despite great hopes, probiotics have not appeared to make a clinically relevant difference in my patients. Though, if they are motivated to try them, I do not discourage them.

Summary

Beyond the already large therapeutic palette of drugs for AD, both topical and oral, we have explored an impressive range of non-pharmacologic options. Some of these are safe and easy, others more onerous. In sifting through the pile, a few stand out as having the right combination of feasibility and therapeutic promise:

- Silk and silver-impregnated clothing, while expensive, appear to offer some tangible benefit with almost no risk and are worth considering in patients with open areas and frequent infections.
- Phototherapy, generally thrice weekly with narrow band UVB, can be an incredibly powerful treatment for those who are not responding adequately to aggressive topical management, and can stave off more powerful immunosuppressant medications in some.
- Dilute bleach baths, aggressive moisturization, and wet-wrap therapy are all mainstays of my general approach to treating moderate-to-severe AD and have reasonably solid evidence to support their use.
- Hypnosis can be of great help especially in those patients where behavioral patterns and stress appear to play a large role in their AD.
- Vitamin D supplementation is inexpensive and safe, and appears to help at least a subgroup of patients, making it a reasonable option to consider.
- Finally, education is critical for all patients with AD, and the development of an "eczema action plan" of some sort can be instrumental in successful treatment. Especially if integrating both pharmacologic and non-pharmacologic measures, in order to keep things straight for both patient and practitioner, a written plan is truly invaluable.

Conclusions

Atopic dermatitis remains a complex and challenging disease. While there are many medicinal therapeutic options, non-pharmacologic therapies remain an attractive adjuvant and occasional replacement for medications. Further understanding of their properties and mechanisms allows for greater insight into the underlying etiopathogenesis of atopic dermatitis, while their judicious use may help balance the risks and benefits of treating this miserable disease.

Compliance with Ethics Guidelines

Conflict of Interest Peter A. Lio has served on boards for Modernizing Medicine and the National Eczema Association, has served as a consultant for Johnson & Johnson & Merck & Co., and has received grant support from the Atopic Dermatitis Foundation.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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